proliferation in smaller islets than in larger islets. In adulthood, however, every beta cell in an islet of arbitrary size ultimately has an equally small proliferation potential. In addition to this limited islet growth, fission of large islets occurred most actively at postnatal week 3, and contributed to maintaining a limited range of islet sizes. On the other hand, in a tumor (insulinoma) progression model, we found unlimited islet growth, with especially accelerated cell proliferation in larger islets. We conclude that islet size is constrained by preferential growth of small islets and fission of large islets in the early postnatal period, and a low rate of proliferation in maturity.

3317-Pos Board B422

In Silico Titration of Biomolecules: Explicit Solvent Constant pH Molecular Dynamics

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The pH is an important parameter in macromolecular systems as it determines the protonation state of ionizable groups and consequently influences the structure, dynamics and function of molecules in solution. In most force field simulation protocols, however, the protonation state of a system (rather than its pH) is kept fix and cannot adapt to changes of the local environment. Here, we present a method to perform molecular dynamics simulations in explicit solvent at constant pH. During the simulation the protonation states of titratable groups are allowed to change dynamically, and the titration curves agree with experiment. Our method is based on the lambda-dynamics approach, in which the dynamics of the titration coordinate lambda is driven by generalized forces between the protonated and deprotonated states. Constant pH simulations can be achieved by accounting for the pH dependence of the hydration free energy. As a benchmark, titration curves of amino acid analogues and a di-peptide, as well as of turkey ovomucoid inhibitor protein were calculated.

3318-Pos Board B423

Estimating the Orientational Entropy of Water at Protein Interfaces

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The entropy of solvents significantly contributes to the stability of the native state of proteins. However, obtaining solvent entropies from molecular dynamics simulations remains a computational challenge. Reasons for this are first, that the phase space of solvent molecules poorly converges because they sample a shallow free energy basin. Second, its dimensionality rapidly grows with the number of molecules.

To address the problem of phase space convergence, we apply the recently introduced approach of permutation reduction. Further, this method maps water molecules such that their resulting trajectories are restricted to a small region of space around a reference position without changing the physics of the ensemble. For density estimation, we adapted the efficient nearest neighbor (NN) method to the curved space of orientations. The NN method is entirely nonparametric and efficient on high-dimensional manifolds. For approximation of the total entropy, we apply the mutual-information expansion (MIE). The MIE is a systematic expansion of the entropy in mutual information terms by splitting the phase space into subsystems with reduce dimensionality.

Orientational entropies of water molecules are estimated by a the combination of these methods. Well-converged and spatially resolved many-body correlations of higher order are captured. The developed method was tested on specific distributions of orientations, the correlated orientations of water molecules from a pure water box, and the correlated orientations of water molecules around the small globular protein Crambin.

We found that orientational correlation is dominated by pair correlations between neighboring water molecules, and drops within the first two water shells. Further, the relative position of water molecules to each other plays an important role in three body-correlations, but their small mutual information suggests that higher order terms are not necessary to capture the orientational entropy of water.

3319-Pos Board B424

Charge Separation and Isolation in Water and Ice Particles on Strong Impacts

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Charge separation is a general phenomenon in nature. There has been vivid speculation and discussion about the mechanism of charge separation in condensed matter on strong impacts at small energies. Here we show that charge separation naturally occurs if water aggregates or particles with embedded charge carriers, e.g. ions, encounter a high energy impact even though no plasma occurs and the involved kinetic energies are much below any molecular ionization energy. We find that the charge distribution in the fragments resulting from a strong impact can simply be described by a three step model. The first level of the model is a simple statistical description of the resulting charge distribution at low salt concentrations by making usage of the Poisson distribution. The second step of describing the charge distribution of the dispersed fragments involves the mutual interaction between the charge particles in the condensed matter, which allows us to describe the charge process at higher salt concentrations. We achieved this by using implicit water Monte Carlo Simulation methods of the charged particles. Finally we included the full dynamics of the separation process into our model by using non-equilibrium Molecular Dynamics Simulations to describe the charge separation at high salt concentrations and high separation process velocities.

We present a microscopic model of the charging mechanism of fragments, that contributes to the understanding of a larger range of phenomena related to charges and charge separation in Nature. With this model we shed light on the charge mechanism of laser desorption experiments and discuss the impact of the current results for particle detection in space and possible implications for lightning formation in the atmosphere.

3320-Pos Board B425

Toward a Unified Model of Molecular Crowding: A Regression Approach to Predict Equilibria and Kinetics of Assembly Systems in Crowded Environments

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Chemistry in living cells functions significantly differently from chemistry in a test tube. One defining characteristic of the intracellular environment is molecular crowding, which can dramatically alter the rates and equilibria of biochemical reactions, potentially either enhancing or inhibiting reactions depending on numerous physical parameters of a given system. However, it is extremely difficult to predict how crowding will quantitatively affect any particular reaction system or which physical factors of the system will be most critical. Sophisticated particle models provide a way to more accurately simulate chemistry in crowded systems, but at a computational cost that makes them infeasible for all but the most trivial reaction systems. With the goal of developing a unified model of molecular crowding, we developed a novel multi-scale approach to predict binding chemistry in crowded media using high-cost particle models of crowded conditions on simple test systems to train predictive regression models that can then be applied to low-cost differential equation or stochastic simulation models of more complicated systems. We show that a polynomial regression model can incorporate several interrelated parameters influencing chemistry under crowded conditions and accurately reproduce thermodynamic binding equilibria from stochastic off-lattice simulations of binding chemistry in crowded media. The model accurately reproduces the results of particle simulations over a broad range of variation of both independent and cross-dependent physical parameters expected to influence the crowding effect. We further show how the approach can be extended to efficiently capture the effects of molecular crowding on kinetic rate parameters. The work thus makes an important step toward the long-term goal of building computational models of reaction chemistry in the cellular environment that are both computationally tractable and predictive for large, complex systems.

3321-Pos Board B426

A Structurally Flexible Protein Backbone for the MARTINI Coarse Grained Force Field

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By reducing the level of description of a system as compared to atomistic models coarse grained (CG) molecular force fields allow simulating larger systems for longer time scales, thereby probing exciting properties of biological systems. It is our constant effort to improve their accuracy and range of applicability.

The MARTINI CG model defines a library of beads or super-atoms corresponding to chemical entities (defined by 3-6 non-H atoms) for which the interaction strengths are parameterized against thermodynamic (partitioning free energies) and structural data extracted from experiments and simulations. Virtually any molecular topology can be built from a combination of beads that reproduces structural and thermodynamic available data for that particular molecule. Molecular topologies are available for a large variety of molecules including lipids, amino acids and proteins, and sugars.

Here we present a refined version of the MARTINI force field for proteins in which restraining the secondary structure is not required anymore. This is achieved by restoring directionality in the backbone interactions. To do so a dipole (two net charges kept at a fix distance) is placed on the peptide bond of the backbone. We show that this simple representation coupled with a rigorous parameterization of the dipole and related bonded/non-bonded interactions is able to capture some essential mechanical and physicochemical properties of the polypeptide backbone. In particular the backbone may access both extended (β-sheet) and compact (α-helix) conformations using a single potential. A few simple test cases are shown to illustrate the structural flexibility of the new backbone and its ability to stabilize secondary structure elements in proteins. The potential is tested with both regular and polarizable MARTINI water models.